A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice.

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AIMS

The aim of this study was to identify what definitions have been published for the term 'deprescribing', and determine whether a unifying definition could be reached. A secondary aim was to uncover patterns between the published definitions which could explain any variation.

METHODS

Systematic literature searches were performed (earliest records to February 2014) in MEDLINE, Embase, CINAHL, Informit, Scopus and Google Scholar. The terms deprescrib* or de-prescrib* were employed as a keyword search in all fields. Conventional content analysis and word frequencies were used to identify characteristics of the definitions. Network analysis was conducted to visualize characteristic distribution across authors and articles.

RESULTS

Following removal of duplicates, 231 articles were retrieved, 37 of which included a definition. Eight characteristics of the definitions were identified: use of the term stop/withdraw/cease/discontinue (35 articles), aspect of prescribing included e.g. long term therapy/inappropriate medications ($n = 18$), use of the term 'process' or 'structured' ($n = 13$), withdrawal is planned/supervised/judicious ($n = 11$), involving multiple steps ($n = 7$), includes dose reduction/substitution ($n = 7$), desired goals/outcomes described ($n = 5$) and involves tapering ($n = 4$). Network analysis did not reveal patterns responsible for variations in previously used definitions.

CONCLUSIONS

These findings show that there is lack of consensus on the definition of deprescribing. This article proposes the following definition: *'Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes'*. This definition has not yet been externally validated and further work is required to develop an internationally accepted and appropriate definition.

Introduction

The term 'deprescribing' (or 'de-prescribing') first appeared in the English health literature in 2003 in an Australian hospital pharmacy journal in an article titled, 'Deprescribing: achieving better health outcomes for older people through reducing medications' [1]. The article outlined the principles of deprescribing, in particular 1) reviewing all current medications, 2) identifying medications to be ceased, substituted or reduced, 3) planning a deprescribing regimen in partnership with the patient and 4) frequently reviewing and supporting the patient.

Medications have many benefits including preventing and curing diseases, prolonging life and improving symptoms [2]. However, medications also carry risks and the risk of adverse drug events increases with polypharmacy and

old age [3, 4]. In developed countries, approximately 20% of all adults are taking five or more medications with increased prevalence in older adults (up to 70% of hospitalized older adults are exposed to polypharmacy) [3, 5]. Additionally, approximately 50% of older adults take a potentially inappropriate medication (PIM) [6, 7]. Polypharmacy and use of PIMs have been associated with increased risk of adverse drug events, geriatric syndromes, hospitalization and mortality and have associated unnecessary financial costs [6–9]. Therefore, providing best possible care through optimal pharmacological treatments will involve both the initiation as well as the cessation of inappropriate or unnecessary medications [10–12].

In clinical practice, medication cessation will, ultimately, be intertwined with the prescribing process. However, the high prevalence of polypharmacy and PIMs and lack of guidelines for people with multi-morbidity and polypharmacy support focusing on desprescribing as a separate entity in research and practice [13–15]. This will require a clear and consistent definition of deprescribing. While the widespread use of this term is new, the practice of withdrawing inappropriate medications is not. Previously employed alternative terms are somewhat ambiguous, for example 'rationalization' and 'de-escalation', while more simplistic terms 'withdrawal' or 'cessation' do not adequately cover the complex process. Establishing a consensus about a deprescribing definition is critical as multiple deprescribing studies are currently underway internationally and the interventions and outcomes are being defined differently, making it difficult to synthesize the emerging evidence [13]. Clinically the definition of deprescribing will have implications for guiding best practice and communication between health care professionals.

The objective of this systematic review was to identify what definitions of deprescribing have been published in the healthcare literature and determine whether a unifying definition could be reached. A secondary aim was to use network analysis to uncover patterns between the published definitions which could explain any variation in characteristics of definitions used.

Methods

A systematic review was conducted in accordance with the PRISMA statement [16].

Search strategy and selection criteria
All scholarly published health literature using the term 'deprescribing' was considered for inclusion in this review regardless of type of publication (e.g. review, commentary, letter, research article, presentation). The search was conducted from database inception to February 2014.

The databases searched were PubMed, International Pharmaceutical Abstracts, Embase, Informit and Scopus.

The terms deprescrib* or de-prescrib* were employed as a keyword search in all fields (there is no Medical Subject Headings (MeSH) or equivalent for deprescribing). Since the earliest articles using the term deprescribing were published in journals which are not indexed in PubMed and to expand the scope of our search outside the traditional databases, a search was also conducted in Google Scholar (deprescribe or deprescribing or de-prescribe or de-prescribing). Full texts of all the articles retrieved from these databases were sought and two authors (ER and DG) independently reviewed all articles for eligibility.

Inclusion criteria
• Use of the term deprescribe/deprescribed/deprescribing OR de-prescribe/de-prescribed/de-prescribing
• Term had to be used in title, abstract, or body of the article
• Clear definition provided for the term (as determined by two independent reviewers)

Exclusion criteria
• Non-English articles
• Use of the term in reference list only
• Subject matter not medication related

Data extraction
Two authors (ER and DG) independently identified all occurrences of the term deprescribe/deprescribing within the included articles and extracted the data using a standardized data collection sheet (Appendix). The data collection sheet was developed and piloted by the first author (ER) and then piloted by the second author (DG) who found it usable and no further changes were made. Where a clear definition was identified, this was extracted, whereas articles which used the term but did not provide a clear definition were excluded from further analysis. Characteristics of a clear definition included 'Deprescribing is …', 'Deprescribing involves …', 'Deprescribing (drug withdrawal) …', and similar. The definition had to be in the same, preceding or proceeding sentence as the term. Additional data extracted was year of publication, type of article (e.g. review, original research), country of author and patient group of interest (e.g. older people, end-of-life). If a reference was given with the definition this too was recorded. Once data extraction was completed, both whether the article was assessed to include a definition and the additional data collected were compared between the two reviewers. Where disparity occurred, this was discussed and a third author (SH) adjudicated.

No assessment of the methodological quality of the studies was conducted as none of the studies was designed to define deprescribing. Additionally, as multiple study types were included (e.g. non-systematic reviews, original research) comparison of quality was not possible.

Analysis

Conventional content analysis The extracted definitions were reviewed and characteristics identified via conventional content analysis [17]. The first reviewer (ER) went over the text word by word, creating the categories and codes for the categories based on the data (i.e. there were no *a priori* categories). As each new piece of text was coded, it was compared with the text already within the category (constant comparison), where no appropriate category existed a new one was formed. Once the first author completed this process, there were seven initial categories. The definitions of the categories and how they should be applied were discussed at length with the second reviewer (DG), after which it was decided that one of the categories needed to be split into two (dose reduction and tapering separated), resulting in eight final categories (see results below). Both reviewers then independently recoded/coded the definitions. Coding was conducted on the definitions extracted only. Final codes were compared between reviewers and non-concordance was resolved through discussion until consensus was reached, with a third reviewer (SH) consulted if necessary. The results are reported descriptively.

Word frequency All extracted definitions were entered into nVivo (QSR International Pty Ltd version 10 0 638 0 SP6) to analyze word frequencies. Minimum word length was four characters, level of exactness was set at 'including stemmed words' with no maximum number of included words. A word cloud (a figure composed of words which are sized based on their frequency in a piece of text) was created within the program and included all words which appeared at least twice.

Network analysis

Network analysis has been applied to the study of scientific collaborations by analyzing and graphically representing collaboration on projects and co-authorship on publications to reveal patterns [18, 19]. It has also been used to look at citation networks to investigate how particular scientific facts are diffused and adopted [20].

We conducted a network analysis by extracting all authors from the articles which provided a definition for deprescribing (author network). Each author is considered a node and ties to other authors indicate co-authorship on one of the included articles. Attributes considered included country of author (determined by affiliation listed on paper), number of publications (within included articles) and the different characteristics of the definitions found in any article on which they were an author.

Secondly, we treated the included papers as nodes (article network), and coded two different types of ties, 1) if the two papers had at least one common author and 2) where one paper cited another with its definition. Country of first author and whether the identified characteristics were included in the definitions were considered as attributes.

Distribution of characteristics throughout the networks were analyzed visually, with the aim of identifying links responsible for use of the characteristic (e.g. citation ties *vs*. common author ties). We also analyzed density (number of ties proportional to the total number of possible ties) and indegree (the number of ties directed to a particular focal node) to explore network and node characteristics. UCINet (version 6 532 Harvard: Analytic technologies) was used for data organization and analyses and Netdraw (version 2 141 Harvard: Analytic technologies) was used for visualizing the networks.

Results

The initial search of the traditional databases returned 138 articles (93 unique articles) and Google Scholar returned 210 results. After removal of duplicates ($n = 117$), the full text was sought for 231 articles. Forty-eight were excluded as they were not relevant (subject matter was not medication related), 35 were excluded as the term was only found in the reference list (i.e. within the title of a reference) and a further 62 were excluded as the term was not found leaving 89 English articles using the term. The earliest article was published in 2003 with use increasing exponentially since then. The majority of articles using the term were published in 2013–14 (42/89).

Of the 89 articles which used the term, 37 provided a definition (Figure 1). Twenty-four of these articles were non-systematic reviews/editorials/commentaries [1, 12, 21–42], three systematic reviews [43–45], five original research articles [46–50], one letter to the editor [51], two newsletters [52, 53], one master thesis [54] and one conference paper [55]. The vast majority of the articles were published by an Australian first author ($n = 26$, five US, two UK, two Canada, one France, one Italy). Fourteen articles focused on older adults, three on people with cancer, one on end of life care, one on older adults with dementia and one on end-stage renal disease. The remainders were non-specific though all mentioned older adults. A total of 18 articles provided one or more reference(s) with the definition. The majority cited Woodward's [1] seminal article ($n = 9$) with the next most commonly cited articles those by Le Couteur *et al.* 2011 [26] ($n = 5$) and Bain *et al.* 2008 [21] ($n = 4$) (Table 1).

Eight characteristics of the definitions were identified (Table 2). The most common characteristic was use of the term stop/withdraw/cease/discontinue which featured in all except two articles. For nine articles, this was the only characteristic coded. The second most common characteristic was that the definition included a description
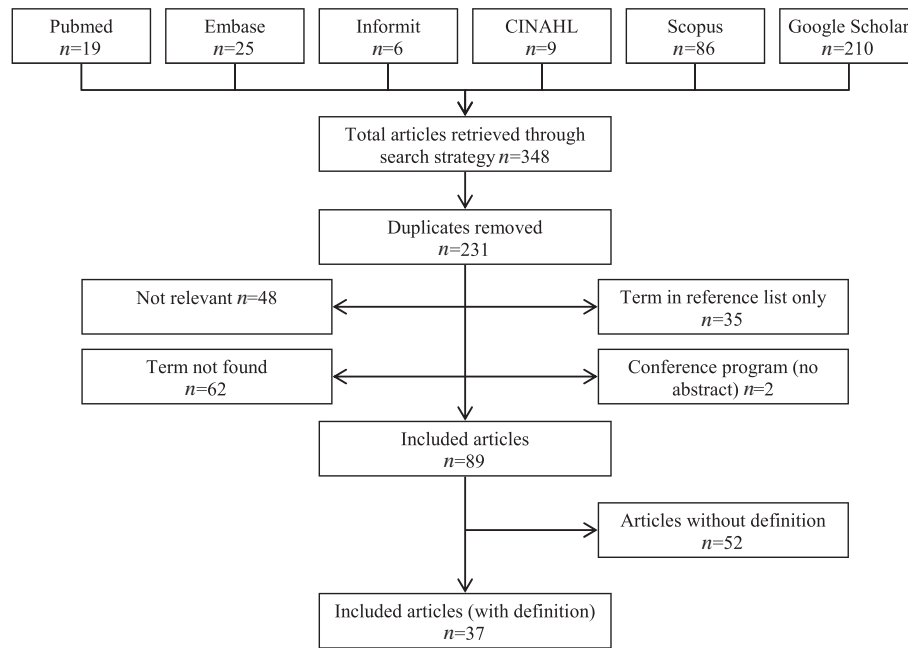
Figure 1

PRISMA flow chart of included articles in the systematic review of the definition of deprescribing

of the type of medication to be ceased including long term therapy and inappropriate medications (included in 18 of the articles).

Word frequency

A total of 196 words (grouped into stemmed words) occurred in all extracted definitions with frequencies ranging from 1 to 47. Seventy-eight words occurred two or more times. The most common words were medication (47), deprescribing (42), patient (19), and process (15). The terms withdraw, cease, discontinue and stop (and grouped stemmed words) occurred a total of 55 times, with withdrawal the most common (14). Other words related to the qualitative analysis of characteristics identified included inappropriate (10), unnecessary (5) and plan (7) (see Figure 2).

Network analysis

Author network Seventy-three authors were included in the analysis for 36 articles (one article was authored by the 'Medicines Management Team', no individuals were named and hence this article could not be included in the author network). The number of publications per author ranged from 1 to 6. The number of ties was 136. Figure 3A shows the author network. Nine authors did not have any ties (single author publications) and seven authors linked two previously unlinked authors together (bridges). The author with the most ties was Le Couteur (11), followed by Gnjidic (9). Density was low at 0.03.

Article network Figure 3B shows the article network. There were 95 ties (70 common author and 25 citation ties) between the 37 articles (nodes) with only five isolates (nodes which are not connected to any other node). Density was 0.09 and 0.02 for the common author and citation ties respectively. The papers with the highest indegree were Le Couteur *et al.* [26] (five citation ties, six common author ties) and Woodward [1] (nine citation ties, one common author tie). Reeve *et al.* [50] was the only article to both cite and be cited. Visually, neither having a common author nor citations appeared to be responsible for use of specific characteristics within a definition and all characteristics appeared in at least two unlinked clusters.

Discussion

To our knowledge, this is the first systematic review to utilize network analysis, in addition to conventional analysis, to uncover patterns between the published definitions of an emerging medical term. A variety of different definitions were identified. Some were simplistic, employing deprescribing as a synonym for stopping drugs, while others included a variety of other factors and encompassing different potential outcomes. Conventional content analysis of the definitions extracted revealed eight characteristics: use of the term stop (or equivalent), a description of the type of prescribing, use of the term process/structured, specifies that withdrawal is planned/supervised, describes deprescribing as multiple

Table 1

Articles providing a definition of deprescribing

Authors, year	Country of first author	Article type	Population of interest	Definition	Reference for definition
Woodward 2003 [1]	Australia	Review	Older adults	The principles of deprescribing include reviewing all current medications, identifying medications to be ceased, substituted or reduced, planning a deprescribing regimen in partnership with the patient and frequently reviewing and supporting the patient.	Nil
Bain KT, Holmes HM, Beers MH, Maio V, Handler SM, Pauker SG, 2008 [21]	US	Review	Non-specific	… deprescribing (or discontinuing) medications.	Nil
Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG, 2008 [43]	Australia	Systematic review	Older adults	… medication withdrawal	Nil
Le Couteur D, Ford GA, McLachlan AJ, 2010 [22]	Australia	Review	Older adults	Withdrawing medications or deprescribing …	Woodward, 2003 [1]
Page M, 2010 [54]	Australia	Other (Master Thesis)	Non-specific	… as removal of drugs or 'deprescribing' …	Nil
Scott I, Jayathissa S, 2010 [23]	Australia	Review	Older adults	… a de-prescribing schedule has been proposed comprising four steps: (i) recognizing an indication for discontinuation (low benefit-risk ratio or no longer needed); (ii) identifying and prioritizing medication(s) to be targeted; (iii) ceasing the medication along with proper planning, communication and coordination with the patient and in concert with other clinicians (iv) monitoring the patient for beneficial or harmful effects of drug withdrawal.	Woodward, 2003 [1]
Boparai M, Korc-Grodzicki B, 2011 [24]	US	Review	Older adults	… deprescribing (or discontinuing) medications.	Bain et al. 2008 [21]
[d] Hardy JE, Hilmer SN, 2011 [25]	Australia	Review	End of life	Deprescribing or ceasing unnecessary or harmful medications ……deprescribing is an individualized process that takes into account the patient's physical functioning, comorbidities, preferences and lifestyle.	Nil
[d] Le Couteur D, Banks E, Gnjidic D, McLachlan A, 2011 [26]	Australia	Review	Non-specific	Here deprescribing is used to define the cessation of long-term therapy, supervised by a clinician.	Nil
Boisdin E, Dufour M, Doucet J, 2012 [46]	France	Abstract (of original research)	Non-specific	The aim of drug 'deprescribing' is to take out drugs which are not necessary or potentially dangerous a patient.	Nil
Geller A, Nopkhun W, Dows-Martinez MN, Strasser DC, 2012 [27]	US	Review	Older adults	… practicing 'medication debridement' within a framework of deprescribing assists in reducing medications … Implementing a schedule of 4 steps can simplify the deprescribing process: (1) recognizing an indication for discontinuation, (2) identifying and prioritizing medications to be targeted for cessation, (3) stopping the medication in collaboration with the patient and other physicians, and (4) monitoring the patient for harmful or beneficial signs of medication withdrawal.	Woodward, 2003 [1]
[d] Gnjidic D, Hilmer SN, Le Couteur DG, 2012a[a] [28]	Australia	Review	Older adults	… judicious cessation of medicines, or 'deprescribing' …	Le Couteur et al. 2011 [26]
[d] Gnjidic D, Le Couteur DG, Kouladjian L, Hilmer SN, 2012b[a] [29]	Australia	Review	Non-specific	Deprescribing trials to reduce medications…	Nil
[d] Hilmer S, Gnjidic D, Le Couteur DG, 2012 [12]	Australia	Review	Older adults	… deprescribing (drug withdrawal) …	Nil

(Continues)

Table 1
(Continued)

Authors, year	Country of first author	Article type	Population of interest	Definition	Reference for definition
Manias E, 2012 [47]	Australia	Original research	Older adults Inpatients, pain management	The practice of de-prescribing, which involved reviewing an older patient's treatment regimen to identify unnecessary or inappropriate medications that could be discontinued or reduced in dose or frequency, influenced nurses' and patients' judgements about whether pain could be tolerated, and their differentiation of pain from discomfort.	Nil
Pond D, 2012 [30]	Australia	Review	Older adults with dementia	The importance of a medication review has recently come to the fore. Such a review may be done by the GP, or in close collaboration with a pharmacist, and any medications that can be reduced or stopped should be identified. This is known as 'deprescribing' and the optimal approach involves reviewing all current medications identifying those to be targeted for cessation and then planning a slow reduction in the offending drugs, in partnership with the patient and their family, and monitoring of adverse effects.	Woodward, 2003 [1]
Russell T, 2012 [31]	Australia	Review	Non-specific	… the concept of deprescribing and that it is a process rather than a single event of stopping a medication.	Nil
Woodward M, 2012 [32]	Australia	Review	Older adults	It is thus essential to avoid unnecessary longer term use of these agents, and to cease/reduce ('deprescribe') them whenever possible.	Nil
Booth J, 2013 [33]	Australia	Review	Non-specific	… deprescribing or ceasing regular medicines.	Reeve et al. 2013c [50]
[d] Hilmer S, Gnjidic D, 2013 [34]	Australia	Review	Older adults	Withdrawal or deprescribing…	Nil
Kouladjian L, 2013 [35]	Australia	Review	Non-specific	… drug withdrawal (or deprescribing) … Deprescribing, also known as ceasing unnecessary or harmful medications … The principles of deprescribing include reviewing all current medications, identifying medications to be ceased, substituted or reduced, planning a deprescribing regimen in partnership with the patient and frequently reviewing and supporting the patient.	Woodward, 2003 [1] Hardy & Hilmer 2011 [25]
Lees J, 2013 [36]	Australia	Review	Older adults with cancer	Medications identified as being unnecessary, inappropriate, or potentially harmful can be considered for discontinuation or so called 'deprescribing'.	Hilmer et al. 2012 [12]
Manias E, Kusljic S, Berry C, Brown E, Bryce E, Cliffe J, Smykowsky A, 2013 [48]	Australia	Original research	Older adults	De-prescribing is the process of ceasing medications when there is ineffective treatment, adverse drug reactions, ineffective treatment or when treatment goals have changed.	Le Couteur et al. 2011 [26]
Medicines Management Team[b], 2013 [52]	UK	Newsletter	Non-specific	De-prescribing - The complex process required for the safe and effective cessation (withdrawal) of inappropriate medications.	Nil
[d] Reeve E, To J, Hendrix I, Shakib S, Roberts M, Wiese M, 2013a[a] [44]	Australia	Systematic review	Non-specific	Deprescribing is the term that has been used to describe the process of medication cessation. The use of this term emphasizes that stopping a medication is more complicated than just not renewing a repeat prescription, or simply telling a patient not to take that medication anymore. … Key elements of a deprescribing process include obtaining an accurate and complete medication list, identifying PIMs, deciding if the inappropriate medication can be stopped at this point in time, planning and communicating a cessation regimen (i.e. with or without tapering) and monitoring, support and review.	Woodward, 2003 [1] Le Couteur et al. 2011 [26] Bain et al. 2008 [21] Scott, I. et al. 2012 [63][c]
[d] Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD, 2013b[a] [49]	Australia	Original research	Non-specific	… the process of medication cessation has been termed 'deprescribing'.	Nil

Table 1
(Continued)

Authors, year	Country of first author	Article type	Population of interest	Definition	Reference for definition
[d] Reeve E, Wiese MD, Hendrix I, Roberts MS, Shakib S, 2013c[a] [50]	Australia	Original research	Non-specific	The term "deprescribing" has been coined to describe a process of optimization of medication regimens through cessation of PIMs. It encompasses review of all medications; identification of PIMs that could be ceased, substituted, or reduced; planning of the deprescribing regimen in collaboration with the individual; and provision of review and support.	Woodward, 2003 [1] Le Couteur et al. 2011 [26] Bain et al. 2008 [21]
Richardson T, Emberley P, Farrell B, Schuling J, Wodchis W, LeBlanc C, Dalgleish C, 2013 [53]	Canada	Newsletter	Non-specific	Deprescribing is the practice of stopping, reducing, or slowly withdrawing medications that are inappropriate, unsafe or ineffective.	Nil
Riker G, 2013 [55]	US	Conference presentation (slides)	Non-specific	Deprescribing: "the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes"	Thompson & Farrell 2013 [39]
Scott I, Gray LC, Martin JH, Pillans PI, Mitchell CA, 2013 [37]	Australia	Review	Older adults	… a structured approach to drug discontinuation (or deprescribing)…	Nil
Somma C, Trillini M, Kasa M, Gentile G, 2013 [38]	Italy	Review	Older adults with end-stage renal disease	… to ensure that polypharmacy is limited to strictly appropriate needs. This novel area of research, which has frequently been called deprescribing, aims to reduce the potentially deleterious consequences of polypharmacy, including herbs, over-the-counter substances and supplements that might occasionally interfere with prescription-only medications, through a strict collaboration between physicians - both general practitioners and specialists - clinical pharmacists and patients.	Schuling et al. 2012 [64] [c]
Turner J, Singhal N, Bell JS, 2013 [51]	Australia	Letter	People with cancer	… an important opportunity for clinicians and patients to consider drug withdrawal or "deprescribing".	Woodward, 2003 [1]
Thompson W, Farrell B, 2013 [39]	Canada	Review	Non-specific	Deprescribing is the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes.	Nil
Alldred D, 2014 [40]	UK	Review	Non-specific	… to describe the cessation of medicines. Iyer et al. in their 2008 paper have described it as 'medication withdrawal in older people' and, more recently, it has been defined as 'cessation of long-term therapy, supervised by a clinician'.	Woodward, 2003 [1] Iyer et al. 2008 [43] Bain et al. 2008 [21] Le Couteur et al. 2011 [26]
Lindsay J, Dooley M, Martin J, Fay M, Kearney A, Barras M, 2014 [45]	Australia	Systematic review	End of life in people with cancer	…"deprescribing" a term used to describe the rationalizationof medicines that provide a limited benefit in patients, due to changing medical and patient factors over time.	Reeve et al. 2013b [49]
Liu L, 2014 [41]	US	Review	Older adults	Deprescribing, the process of tapering, withdrawing, discontinuing, or stopping medications, is important in reducing polypharmacy, adverse drug effects, inappropriate or ineffective medication use, and costs.	Gnjidic et al. 2012b [29]
[d] Reeve E, Wiese MD, 2014 [42]	Australia	Review	Non-specific	Deprescribing is a holistic process of medication cessation that encompasses gaining a comprehensive medication list, identifying potentially inappropriate medications, deciding if the identified medication can be ceased, planning the withdrawal regimen and monitoring, support and follow-up. … to describe the process of cessation of medications that are not providing a benefit to the patient or are exposing them to unacceptable risks.	Nil

[a]Letters a, b, c etc. are denoted where a primary author has published two or more included articles in the same year, these related to those used in the article network. [b]Author of this article is denoted at 'Medicines Management Team' No individual author information could be found. [c]These articles were retrieved in our original search strategy but were excluded due to absence of a clear definition. [d]One or more of the authors of this article is an author of this systematic review.

Table 2

Characteristics of the definitions of deprescribing

Characteristic (code)	Number of articles containing the characteristic in the definition of deprescribing	References	Example
Uses the term stop/cease/ discontinue/withdraw/remove or other synonyms (STOP)	35	[1, 12, 21–37, 39–44, 46–55]	'… deprescribing (or discontinuing) medications.' [24] '…deprescribing (drug withdrawal)…' [12]
A description of the type of medication to be ceased (e.g. long term, inappropriate medications) (PIMS)	18	[23, 25, 26, 32, 33, 35, 36, 40–42, 44–48, 50, 52, 53]	'…cessation of long term therapy…' [26] '… medications that are inappropriate, unsafe or ineffective.' [53]
Uses the term 'process' or 'structured' (PROCESS)	13	[25, 27, 31, 37, 39, 41, 42, 44, 48–50, 52, 55]	'De-prescribing is the process of ceasing medications…' [48] '…a structured approach to drug discontinuation (or deprescribing)…' [37]
Withdrawal is planned/ supervised/judicious (PLAN)	11	[1, 23, 26, 28, 30, 35, 38, 40, 42, 44, 50]	'…supervised by a clinician.' [40] '…planning and communicating a cessation regimen…' [44]
Describes deprescribing as involving multiple steps (STEPS)	7	[1, 23, 27, 30, 35, 42, 50]	'The principles of deprescribing include reviewing all current medications, identifying medications to be ceased, substituted or reduced, planning a deprescribing regimen in partnership with the patient and frequently reviewing and supporting the patient.' [1] 'It encompasses review of all medications; identification of PIMs that could be ceased, substituted, or reduced; planning of the deprescribing regimen in collaboration with the individual; and provision of review and support.' [50]
Includes dose reduction and/or substitution (REDUCE)	7	[1, 30, 32, 35, 47, 50, 53]	'…identifying medications to be ceased, substituted or reduced…' [35]
Definition includes a goal or desired outcome of deprescribing (GOAL)	5	[38, 39, 41, 50, 55]	'…aims to reduce the potentially deleterious consequences of polypharmacy…' [38] '…with the goal of managing polypharmacy and improving outcomes…' [39]
Uses the term 'taper' (TAPER)	4	[39, 41, 44, 55]	'…the process of tapering…' [55]

steps, includes dose reduction and substitution, includes a goal or outcome of deprescribing and reports tapering is required. Quantitative word frequencies supported several of the characteristics, including high use of the word withdrawal (and synonyms) as well as process and inappropriate/unnecessary.

Visual inspection of the network analysis provided little insight into the patterns of characteristics of the definition of deprescribing observed across the articles. The density in both types of networks (author network and article network) was very low with few bridges observed indicating that there was limited interaction between clusters. In the analysis of papers as nodes neither the citation ties nor the common author ties seemed to be responsible for the pattern of characteristics. This indicates that other, un-captured factors are responsible for the variations in characteristics used. Social (i.e. non-academic) relationships may be present, authors may have co-authored on papers not included in our analysis, authors may have read papers and not specifically cited them with the definition or authors

may have independently decided on characteristics to include based on their personal opinion. Alternatively, the academics researching and publishing in this area may also be clinicians and/or involved in educational activities (e.g. presenting at conferences or workshops, clinical teaching or developing and delivering curricula) and it is possible that definition characteristics were disseminated through these mediums. However, one included article [55] was a conference presentation identified through our Google Scholar search. It has also been previously observed that papers may cite a previous article but distort the content, termed 'citation diversion' [20].

Strengths and limitations

The strengths of this study include a rigorous systematic review approach with two reviewers independently determining eligibility, extracting the data and conducting the coding. The results of our qualitative method of content analysis (which may be considered subjective) were consolidated with an objective measure of word frequency and creation of a word cloud. This study also employed a

Figure 2

Word cloud of definition of deprescribing (words which occurred two or more times, stemmed words grouped, minimum four characters)

novel method of network analysis to attempt to understand the derivation of a definition. The results of the network analysis were limited due to being unable to identify the authors of one of the articles [52] and by only analyzing collaborations on the included articles. The finding that the variations cannot be explained by citation or collaborations is noteworthy.

While we engaged in a systematic process involving two individuals independently identifying the articles and extracting the data, there are several limitations to this study. In our effort to not extrapolate the meanings of other authors we only included articles where the definition was clear, and only assigned characteristics to the extracted definition. It is therefore possible that the included articles provided more explanation of steps required for deprescribing or the rationale for deprescribing in other sections of the article. We did not perform 'participant checking' (i.e. contacting the original authors) which would have strengthened our analysis. There is also room for debate within the categories as to the meanings of specific terms. For example, whether supervision and planning cover the same concept, and whether using the term 'process' should have been grouped with the characteristic 'steps'.

No assessment of the quality of the papers was conducted with seemingly equal weighting applied to all the studies. However, as the definition was not the focus of any of the included studies, study quality was unlikely to reflect the quality of the definition used.

The proposed definition has not been externally validated, though the rationale for the characteristics included are provided below. Several important limitations of our proposed definition need to be highlighted. Firstly,

the majority of included publications utilizing the term 'deprescribing' are Australian, as are the authors of this article. Additionally, this is a review of the definition of an English word and as such was limited to articles published in English. There may be words for comparable processes in other languages that were not captured by this review. Therefore, the international generalizability of our definition is limited. Future research should be conducted into appropriate translations and comparisons with non-English definitions. Secondly, publications using the term, 'deprescribing' have increased significantly since the conduction of our systematic review (February 2014), and as such there are likely to be more published definitions of this emerging term than those captured here. While this dates our review, it also highlights the need for a unifying definition. The definition may also change over time as new research generates evidence on any benefits of deprescribing and on the best methods of implementation of deprescribing into practice. There is also the potential for bias within this review and relating to our proposed definition as both reviewers (ER and DG) and the senior author (SH) used to gain consensus in the coding have previously published on the topic of deprescribing and indeed are first authors of several of the papers included in this review (*n* = 8). We have highlighted those included articles in which one or more of the present study article authors was a contributor (Table 1) and the authors (Reeve, Gnjidic and Hilmer) can be identified in the network figure (Figure. 3A) to view their connections. Additionally, we have presented all the text (definitions) used to create the characteristics in Table 1 and as such readers can refer to this to make their own judgements. Prior to data extraction and analysis, the two reviewers (ER and DG) had not published nor collaborated on a project together and there was no tie between these two in our author network analysis. There are also no characteristics that come exclusively from authors of this paper. Because of the above mentioned limitations, further work is required before our proposed definition can be recommended for international adoption into research and practice. We suggest that the next step would be to conduct a consensus approach with international experts to review and revise the proposed definition.

Proposed definition

Based on our findings the following definition is proposed:

Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes.

This definition was developed through discussion amongst authors using the results of the systematic

A

Shapes of nodes are country of author
- Australia
- US
- UK
- Canada
- Europe (excluding UK)
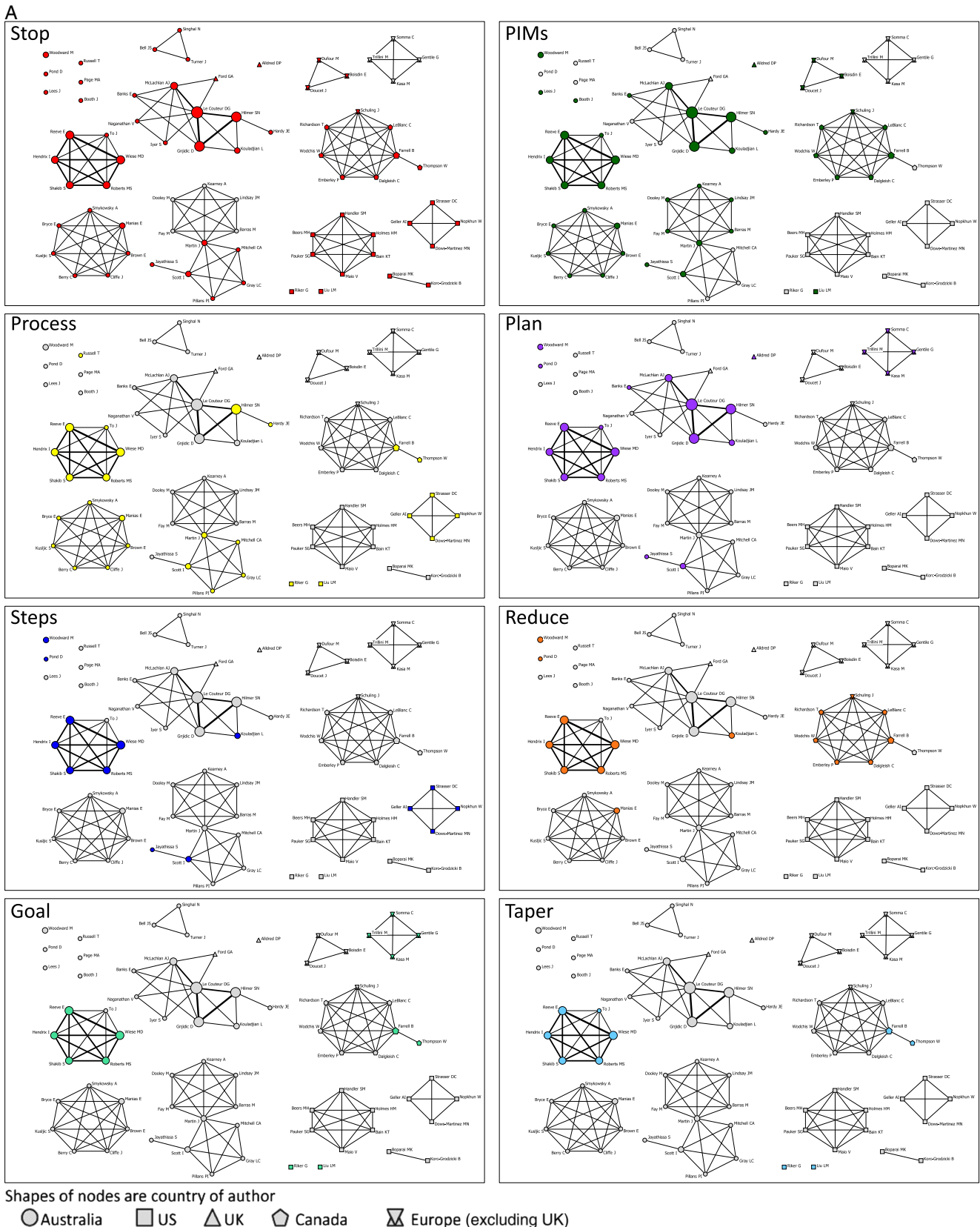
Figure 3

Network analysis of the definition of deprescribing. A) author network, Nodes are sized by number of included articles authored. B) article network, Nodes are sized by indegree of citation ties. Colours of nodes represent definition characteristics: grey node = characteristic not present, coloured node = characterirstic present.
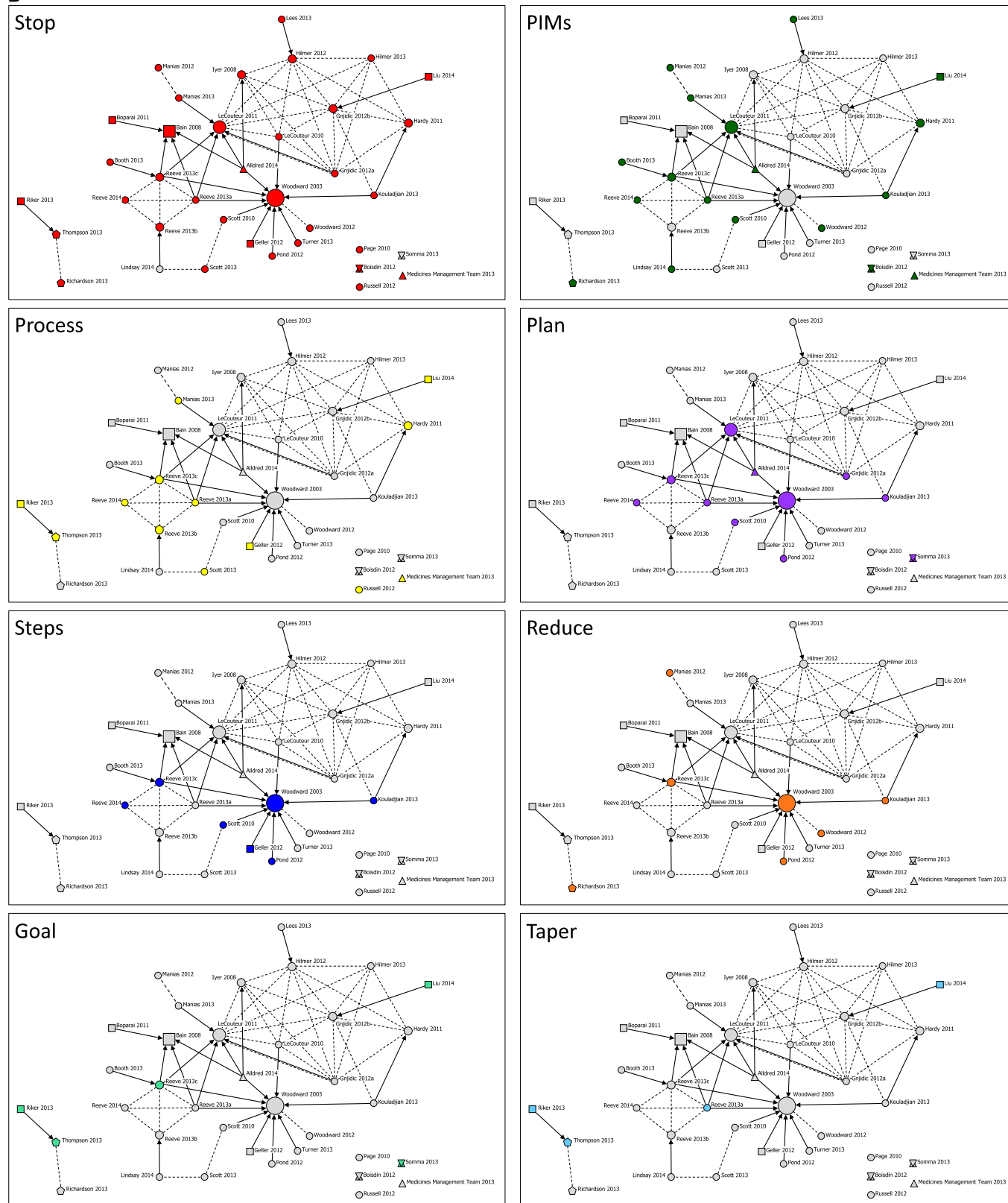
B

Figure 3
(Continued)

review. It was a dynamic process with multiple possible definitions discussed. Firstly, the characteristics were discussed and it was decided that the most commonly identified characteristics should be included. Then the remaining characteristics were reviewed and appropriateness of including in the definition was assessed against clinical and pharmacological considerations. The most commonly used words identified through the word frequency analysis were reviewed to determine if they supported the included characteristics and to inform choice of wording (e.g. the term withdrawal was chosen for the characteristic 'stop' as it was the most commonly used). The purpose of the network analysis was primarily to uncover patterns between the published definitions which could explain any variation in characteristics across papers. It was, however, also utilized in proposing a definition to ensure that included characteristics did not come from a single author group/paper or from a single country.

This definition encompasses five of the eight characteristics identified. The first characteristic included in our definition is 'process'. Including this word in the definition highlights that deprescribing is not a single act and multiple steps are involved, similar to the prescribing process. It was also the fourth most used word among the definitions. Use of this term also covers the characteristic of 'steps'. Various research supports that a process is required for safe and effective deprescribing [15]. The characteristic of medication cessation is at the core of deprescribing (regardless of the specific word used, however, withdrawal was the most favoured). This characteristic occurred in all but two articles, where medication cessation was implied: limiting polypharmacy [38] and rationalization of medications [45]. Two of the included characteristics, that the medication to be ceased is inappropriate and that it is supervised by a health care professional, are important to distinguish deprescribing from what it is not – non-adherence or denying effective treatment. An inappropriate medication is any drug in which the risks outweigh the benefits or where these do not align with goals of care. Thus, it encompasses both ineffective or unnecessary treatment and those treatments which are high risk [56]. However, various definitions exist in the literature and so inclusion of this term in our definition may be contentious as there is potential for misinterpretation. The final characteristic of the desired outcomes/goals was included to justify the reasons behind deprescribing, to both health care professionals and patients.

Dose reduction and substitution may be more accurately considered a part of optimal prescribing and not specifically deprescribing [21, 57]. Though, as previously mentioned, deprescribing too can be considered a part of the prescribing process. Even though dose reduction can be necessary and beneficial in any patient, but particularly older adults due to pharmacokinetic and pharmacodynamics changes, this should occur to improve the risk benefit profile and not in the situation where the medication should be withdrawn as it is inappropriate regardless of dose (i.e. if a medication is truly inappropriate, dose reduction would not be considered as an optimal outcome). Additionally, dose reduction does not fit the aim of reducing polypharmacy. While tapering is required for a subset of medications it is not always necessary, for example long term corticosteroid use should be tapered prior to cessation while bisphosphonates may be stopped abruptly [21].

Implications

Optimizing medication therapies is complicated and efforts to improve the current state of medication utilization are required [58]. In 2008 Iyer et al. [43] published a systematic review into the success and outcomes of medication withdrawal in older adults. They concluded that there was some evidence to support the benefits of deprescribing (e.g. resolution of adverse drug effects) and a lack of significant harm. Since Iyer's review, evidence continues to accrue to support the premise that deprescribing results in clinically significant benefits with minimal harm. However, the evidence is generally limited to specific drug classes [13, 59]. For example, a 2013 Cochrane review [60] found that chronic antipsychotics used for neuropsychiatric symptoms of dementia can be safely withdrawn without detrimental effects on behaviour, and a recent randomized clinical trial found that withdrawal of statins in the setting of a life-limiting illness resulted in improved quality of life and reduced medication costs [61]. While it is still unknown what is the most effective way to implement deprescribing in practice [62], this term and a consistent definition will have important implications for both research and practice. While Woodward's seminal article [1] is the most highly cited, its definition consists of principles/steps for conducting deprescribing and only included four of the eight characteristics that were identified across all the included articles and therefore has not been employed consistently (even among the articles which cited it). Alternative terms such as 'medication withdrawal' or 'medication cessation' are limited and multiple variations exist. This makes searching for research on this subject very difficult, and this difficulty has been highlighted in several systematic reviews [43, 44]. Use of the term deprescribing, with a consistent definition, will mean that designing, identifying, comparing and, potentially, synthesizing research on this concept will be more effective. From a clinical perspective, a consistent definition will have implications for guiding best practice (i.e. the characteristics 'supervised', 'process' and 'of an inappropriate medication'), guideline development, communications between health care professionals and promotion to health care professionals (the characteristic 'goal' may serve as a reminder and an encouragement to consider deprescribing more regularly in practice).

Conclusions

Reaching a consensus on a standard definition for 'deprescribing' is essential to inform research on deprescribing and clinical practice. This article proposes a definition based on all those used in academic literature to the time of this review: '*Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes*'. This definition has not yet been validated. Several included and non-included characteristics may be contentious. The term 'inappropriate' is imperfect due to its own variations in definition and the exclusion of 'dose reduction and substitution' and 'tapering' from the definition may be questioned by some, although the justifications for these decisions are provided. The definition of deprescribing, a term that originated in Australia and has subsequently been used internationally, may be biased towards Australia due to the large proportion of publications by Australians and indeed the authors of this article are Australian. Future work should involve international review of the applicability and appropriateness of the definition characteristics and expert consensus to develop an internationally accepted definition.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf587 (available on request from the corresponding author) and declare no support from any organization for the submitted work. Dr Reeve reports support from a grant from the Australian National Health and Medical Research Council Cognitive Decline Partnership Centre during the conduct of this study and Dr Gnjidic reports support from the Australian National Health and Medical Research Council Early Career Fellowship. There are no other financial relationships with any organizations that might have interest in the submitted work in the previous 3 years and no other relationship or activities that could appear to have influenced the submitted work.

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Data access and responsibility

All individuals listed as authors have contributed substantially to the concept and preparation of this manuscript. ER and DG conducted the systematic review, data extraction and content analysis. ER and JL conducted network analysis. ER drafted the manuscript. ER, DG, JL and SH conducted revision of the manuscript (revising it critically for important intellectual content), gave approval of final version and are in agreement to be accountable for all aspects of the work.

ER had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Additionally, DG had full access to the data pertaining to the systematic review and conventional content analysis and takes responsibility for the integrity of these data and the accuracy of the data analysis. JL had full access to the data pertaining to network analysis and takes responsibility for the integrity of these data and the accuracy of the data analysis.

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